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**(54) Title:** PREPARATION FOR TOPICAL APPLICATION TO THE MALE SEXUAL ORGAN**(57) Abstract**

A pharmaceutical preparation for topical application to the male sexual organ having as active ingredients at least one vasodilator from the group including glyceryl trinitrate, aminophylline, co-dergocrine mesylate, and isosorbide dinitrate and an aloe extract together with adjuvants to enhance penetration and stability to form an aqueous cream or gel packaged in unit dosage form.

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## PREPARATION FOR TOPICAL APPLICATION TO THE MALE SEXUAL ORGAN

### Background of the Invention

This invention relates to a preparation of topical agents for application to the male sexual organ for treatment of male erectile dysfunction or impotence. Male erectile dysfunction is a widespread problem in human males leading to the inability to have sexual intercourse. Due to the dysfunction, there may be resultant psychological damage, or even impairment of procreation requiring artificial insemination procedures. Causes of male erectile dysfunction can be either psychological or physical in nature.

Current effective treatment modalities for erectile dysfunction involve invasive or mechanical techniques, such as vacuum constriction devices. Numerous vasoactive agents have been administered intracavernously to induce erection including sodium nitroprusside, papaverine and prostaglandin E1. This unpleasant route of administration, or the use of vacuum constriction devices, is not well accepted by patients which leads to a high incidence of non-compliance with these therapies.

Another drug therapy (a metabolic precursor to prostaglandin E1) has been administered transeurethrally. Studies have shown a 65% success rate for patients using the active drug versus a 19% for those using a placebo. The disadvantages of the product include

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an unpleasant administrative route and high adverse experience profile, 32% penile pain for patients using the active drug versus 3% for those using the placebo and 5.8% vaginal burning or itching in sexual partners with the active drug versus 0.8% with the placebo.

Topical prostaglandin E1 has also been reported to be successful in patients with spinal injuries producing significant increases in systolic arterial flow rates. Topically administered papaverine and minoxidil do not significantly improve erectile dysfunction. A nitroglycerin plaster (transderm-nitro with a dosage of 10 milligrams within 24 hours) produced a positive erectile effect in 12 of 17 spinal cord injury patients who were previously treated successfully with intracavernous papaverine. Only 5 of the 17 patients were sufficiently stimulated to allow vaginal penetration.

Several new oral drugs which appear promising are currently under development or in distribution. One such oral medication, Viagra (sildenafil) was approved for distribution and sale in April 1998. This phosphodiesterase inhibitor has demonstrated 65% to 85% effectiveness for the active drug versus 39% for the placebo. However, 6 of 12 patients have exhibited mild side effects. Another oral medication, Vasomax (phentolamine) is a fast-dissolving tablet currently in clinical trials. This drug is predicted to be helpful in 40% of men with moderate impotence.

Scientific evidence strongly suggests that a topical cream, like that described herein, is an effective and much needed therapy. The simple application of an effective topical cream just prior to intercourse would be an ideal solution for treating male impotence. The cream appears to be safe and effective while not requiring painful invasive techniques, risky systemic oral administration, or the use of uncomfortable mechanical devices. Preparations such as the topical cream discussed herein, in many cases, overcome erectile dysfunction.

The topical agents which have previously been described and used for treating male erectile dysfunction include a group of vasodilators (papaverine and other similar drugs) plus a transdermal carrier, dimethylsulfoxide, are discussed in U.S. Patent 4,801,587 [Voss, et al.]. Further, a combination of nitroglycerin (as a vasodilator) and caffeine (as a vasoconstrictor), in combination with a dimethylsulfoxide, was described in U.S. Patent 5,059,603 [Reuben]. Nitroglycerin was also used with other enhancers and described in U.S. Patent 5,698,589 [Allen]. In combination, a topical composition of a vasodilator (papaverine), a gel enhancer (cyclodextrin), a vasoconstrictor (epinephrine) and an alphablocker (phentolamine) are described in U.S. Patent 5,256,652 [El-Rashidy]. Other compositions include combinations of piperoxan, postaglandins and vasodilators are described in U.S. Patent 5,583,144 [Kral]. A broad group of organic nitrite compounds are described in U.S. Patent 5,646,181 [Fung, et al.] and a selection of S-nitrosothiol compounds are described in U.S. Patent 5,648,393 [Stamler, et al.] for use in various topical formulations.

Other pharmaceutical preparations formulated as topical applications are described in U.S. Patent 4,293,565 [Cordes, et al.] where the isosorbide dinitrate (2 - 20% active ingredient) is used for the treatment of angina. Further, topical compositions containing C8-C24 fatty acid esters (including stearic acid) and a list of therapeutic agents including reproductive modulators, growth promoters, antihelminthincs, antibiotics, antiparasitics, bronchodilators (including aminophylline), cardiovascular agents, anti-allergy, and micronutrients are discussed in U.S. Patent 5,332,577 [Gertner, et al.].

Aloe vera has been used in combination with other ingredients in certain topical formulations. Aloe vera is a natural plant abstract obtained from the common aloe plant, a type of lily, whose natural healing properties have been used for a variety of treatments, i.e.

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relieving itching from insect bites and allergic reactions. A combination of aloe and benzoyl peroxide or aloe and acetylsalicylic acid have been described for treatment of razor bumps. Combinations of aloe and various anti-inflammatory agents or analgesics have also been described in the medical literature.

It is an object of the present invention to provide a pharmaceutical preparation, in combination, of topical agents for application to the male sexual organ for the treatment of male erectile dysfunction or impotence.

It is a further object of the present invention to provide a pharmaceutical preparation of one or more vasodilators and an aloe extract as a topically applied aqueous cream or gel for treatment of male erectile dysfunction or impotence.

It is still a further object of the present invention to provide a pharmaceutical preparation of two or more vasodilators, in combination, and an aloe extract as a topically applied aqueous cream or gel for treatment of male erectile dysfunction or impotence.

Other objects will appear hereinafter.

#### Summary of the Invention

Erectile dysfunction is a widespread problem with human males. The consequences result in psychological damage and in many cases frustrates the normal fertilization processes so that artificial insemination procedures must be used if procreation is required. The causes of this dysfunction may be physical or mental. Procedures for overcoming this problem have been proposed which can involve the surgical implantation of stiffening devices. Chemotherapeutic approaches have been proposed which require the injection of vasodilator compositions immediately prior to intercourse. The injection takes place on or near the penile

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shaft. Neither procedure is attractive and both approaches can result in revulsion or distress on the part of the partners involved. Other methods propose topical application of compositions containing vasodilators. Dimethylsulphoxide is a preferred component of such compositions due to its ability to carry compounds through the skin barrier. Unfortunately, this compound is considered to be deleterious to health. The present invention provides a preparation for topical application to the male sexual organ which causes the erectile tissue to engorge and, in many cases, enable normal sexual intercourse to take place which does not use dimethylsulphoxide as a carrier.

The preparation for topical application to the male sexual organ comprises, as active ingredients, at least one vasodilator and an aloe extract formed into an aqueous cream or gel. The preparation also includes adjuvants such as one or more of stearic acid, triethanolamine, silicone oil, cetyl alcohol, glycerol, acidic carboxyvinyl gelling agents, methyl cellulose, wax emulsifiers, methyl paraben and propyl paraben so as to form the aqueous cream or gel. The aloe extract is prepared using an extract prepared from the plant aloe ferox which contains at least 30% by weight amino acids and also includes polysaccharides. The vasodilator may comprise one or more of the following chemical compounds, in combination, glycetyl trinitrate, isosorbide dinitrate, aminophylline and co-dergocrine mesylate. To assist penetration, the adjuvants may include one or more penetration enhancers such as propylene glycol, isopropyl palmitate and isopropyl myristate. The substantially thixotropic cream or gel is supplied in unit dosage form. The preparation is manufactured by mixing the active ingredients as a finely divided solid or as a solution to form a solution or dispersion in an aqueous cream or gel composition. The aloe extract and one or more gelling agents are prepared as one batch, a

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soap composition is prepared as a second batch and thereafter the two batches are mixed to form a homogeneous mixture to which the vasodilator is admixed.

#### **Detailed Description of the Preferred Embodiments**

The following detailed description is of the best presently contemplated mode of carrying out the invention. The description is not intended in a limiting sense, and is made solely for the purpose of illustrating the general principles of the invention. The various features and advantages of the present invention may be more readily understood with reference to the following detailed description.

According to the present invention, there is provided a preparation for topical application to the male sexual organ comprising as active ingredients at least one vasodilator and an aloe extract together with adjuvants to form an aqueous cream or gel. The vasodilator may be any of the compounds known to have this property such as glycetyl trinitrate and isosorbide dinitrate or compositions supplied for this purpose such as aminophylline, a combination of theophylline and ethylene diamine, and co-dergocrine mesylate, a combination of dihydroergogormime mesylate and dihydroergocrinne mesylate with alpha and beta dihydroergocrytine mesylate. Combinations of such active ingredients with glycetyl trinitrate (nitroglycerin) may also be used.

The aloe extract is preferably one prepared using an extract prepared from the plant aloe ferox. Such extracts contain at least 30% amino acids and have a high level of polysaccharides. Extracts from some other species of aloe may be used such as those called aloe vera and also aloe peryi.

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The adjuvants used to ensure consistency and easy application of the preparation include stearic acid, triethanolamine, silicone oils, cetyl alcohol, glycerol, acidic carboxyvinyl; gelling agents (such as those sold under the trademark Carbopol<sup>®</sup>), methylcellulose, wax emulsifiers (such as those sold under the trademark Brij<sup>®</sup>); and antibacterial and antifungal preservatives such as propyl and methyl paraben. Carbopol<sup>®</sup> 940 is a preferred ingredient and may be described as a carbomer which is a synthetic high molecular weight polymer of acrylic acid cross-linked with either a sucrose or allyl ethers of pentacrythrol used as a gelling agent. Brij<sup>®</sup> 99 is a brand name for a wax emulsifier to produce a stable oil/water mixture.

The penetration and absorption of the active components through the skin can be enhanced by the inclusion of compounds such as propylene glycol, isopropyl palmitate, isopropyl myristate, glycerin and a silicone liquid supplied by Dow Corning under the designation Silicone 344; all of which are considered to be penetration enhancers. Other ingredients can include fragrances and/or colorants.

The active ingredients are mixed as a finely divided solid, or as a solution, to form a solution or dispersion in an aqueous cream or gel composition. When appropriate, such as when using Carbopol<sup>®</sup> type thickeners, pH adjustment is carried out to provide a suitable consistency for topical application. Preferably the preparation is thixotropic so that the effect of temperature variations on viscosity and flow are minimized and subsequent to application the preparation does not flow.

In a preferred method, the aloe extract and suitable gelling agents are prepared in one batch and a soap composition (of adjuvants) in a separate batch. The two components are mixed to form a homogenous mixture at which stage the vasodilator is admixed followed by any fragrance and/or colorant to complete the composition for packaging in dosage form.

The final preparation is preferably packaged in a unit dosage form so that application can be controlled. Such packaging can comprise packets or tubes containing a measured quantity of the cream or gel, preferably one or two grams. The packets are constructed in a conventional manner from polymer film with tags or other known means to assist bursting at one end enabling the contents to be extruded by squeezing the body of the packet. Alternatively, the preparation may be enclosed in small tubes with removable caps. A further alternative is to encapsulate the unit dosage in a soft gel capsule or to apply the unit dosage in a pre-measured aerosol spray. To maintain a partial or complete erection, a pre-measured quantity of the preparation may also be enclosed within a condom.

In order that the invention may be clearly understood, a series of preparations according to the invention will now be described.

#### EXAMPLE I

A cream composition was prepared containing the following ingredients as percentages by weight:

aminophylline	vasodilator	2.50
isosorbide dinitrate	vasodilator	0.50
co-dergocrine mesylate	vasodilator	0.10
aloe extract 10:1	enhancer	15.00

these active ingredients were formed into a cream by admixture with:

stearic acid	24.00
triethanolamine	2.20
Silicone 344	2.00
cetyl alcohol	1.00
glycerol	0.60
methyl paraben	0.25
fragrance	0.15
colorant	0.05

The cream was completed by the incorporation of 51.65% demineralized water.

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The active ingredients and the soap composition were separately mixed before admixture in a manner conventional in the cosmetics industry.

#### EXAMPLE II

A cream composition was prepared containing the following ingredients as percentages by weight:

glyceryl trinitrate	vasodilator	10.00
(as 10% solution in propylene glycol)		

aloe extract	enhancer	15.00
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these active ingredients were formed into a cream by admixture with:

isopropyl palmitate	2.00
triethanolamine	1.20
Carbopol 940	0.70
polyethylene glycol	0.60
Brij 99	0.50
methyl cellulose	0.25
propyl paraben	0.15
methyl paraben	0.15
fragrance	0.15
colorant	0.05

The cream was completed by the incorporation of 69.00% demineralized water.

#### EXAMPLE III

A gel composition was prepared containing the following ingredients as percentages by weight:

aminophylline	vasodilator	2.50
isosorbide dinitrate	vasodilator	0.50
aloe extract	enhancer	15.00

These active ingredients were formed into a gel by admixture with:

triethanolamine	2.00
Silicone 344	2.00
glycerin	2.00
Cremophor RH40	0.80
methyl paraben	0.20

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fragrance	0.15
colorant	0.05

The gel was completed by incorporation of 74.00% demineralized water.

#### EXAMPLE IV

A gel composition was prepared containing the following ingredients as percentages by weight:

glyceryl trinitrate	vasodilator	9.00
(as 10% solution in propylene glycol)		
aminophylline		2.50
aloe extract	enhancer	15.00

These active ingredients were formed into a gel by admixture with:

triethanolamine	2.00
Silicone 344	2.00
glycerin	2.00
Cremophor RH40	0.80
Carbopol 940	0.80
methyl paraben	0.15
fragrance	0.15
colorant	0.05

The gel was completed by the incorporation of 65.55% demineralized water.

Other combinations of the vasodilators may be combined in accordance with the teachings of the present invention. In each of the Examples, the aloe extract was a composition sold under the name "aloe vera 10:1" produced by extraction from aloe ferox. The extract was ten times the constituent strength of standard "aloe vera" compositions.

In use, two grams of one of the cream or gel compositions was applied to the glans penis and penile shaft and gently massaged into the skin. The effect was to produce an erection of the penis which was maintained for approximately 45 minutes. In an alternative mode of use, one gram of the cream or gel was applied approximately two hours before an erection was desired. A second application was applied 30 minutes later resulting in an

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erection a short time later. The effect achieved by use of the cream or gel is enhanced by the types of audio, visual and tactile stimuli which in many cases initiate a penile erection.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, the described embodiments are to be considered in all respects as being illustrative and not restrictive, with the scope of the invention being indicated by the appended claims, rather than the foregoing detailed description, as indicating the scope of the invention as well as all modifications which may fall within a range of equivalency which are also intended to be embraced therein.

We claim:

1. A preparation for topical application to the male sexual organ comprising as active ingredients at least one vasodilator and an aloe extract together with adjuvants to form an aqueous cream or gel.
2. The preparation as claimed in Claim 1, in which the vasodilator comprises two or more in combination from the group consisting of glyceryl trinitrate, aminophylline, co-dergocrine mesylate, and isosorbide dinitrate.
3. The preparation as claimed in Claim 1, in which the vasodilator comprises one or more from the group consisting of aminophylline, co-dergocrine mesylate, and isosorbide dinitrate.
4. The preparation as claimed in Claim 1, in which the aloe extract is prepared using an extract prepared from the plant aloe ferox.
5. The preparation as claimed in Claim 1, in which the aloe extract contains at least 30% by weight amino acids and also includes polysaccharides.
6. The preparation as claimed in Claim 4, in which the aloe extract contains at least 30% by weight amino acids and also includes polysaccharides.
7. The preparation as claimed in Claim 1, in which the adjuvants comprise one or more from the group consisting of stearic acid, triethanolamine, silicone oil, cetyl alcohol, glycerol, acidic carboxyvinyl gelling agents, methyl cellulose, wax emulsifiers, methyl paraben and propyl paraben.
8. The preparation as claimed in Claim 7, in which the adjuvants further comprise one or more from the group consisting of propylene glycol, isopropyl palmitate and isopropyl myristate.

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9. The preparation as claimed in Claim 1, in which the preparation is substantially thixotropic.
10. The preparation as claimed in Claim 1, being in unit dosage form.
11. A method of manufacturing a preparation for topical application to the male sexual organ, wherein the active ingredients are mixed as a finely divided solid or as a solution to form a solution or dispersion in an aqueous cream or gel composition.
12. The method as claimed in Claim 11, wherein the aloe extract and one or more gelling agents are prepared as one batch, a soap composition is prepared as a second batch and thereafter the two batches are mixed to form a homogeneous mixture to which at least one vasodilator is admixed.
13. The method as claimed in Claim 11, wherein the manufactured preparation is packaged in unit dosage form.